## Research article

# The effects of tocilizumab on clinical and laboratory features of patients with severe COVID-19: a single center experience

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**Abstract**

**Objective:** Cytokine storm is considered as the immune hyperinflammatory process which may deteriorate the course of COVID-19. Interleukin (IL-6) inhibitors can be used in severe COVID-19 patients due to their anti-inflammatory and anti-immune effects. We aimed to assess the therapeutic effect of tocilizumab (Actemra) in patients with severe COVID-19 pneumonia.

**Methods:** Overall, 1382 patients were admitted to a temporary hospital during July outbreak of COVID-19. Of these, 282 patients were hospitalized. Baseline clinical, radiological and laboratory data were collected from patient records. Laboratory markers prior to discharge were also collected. Wilcoxon rank sum test was conducted to show the significance of change of laboratory markers.

**Results:** Eleven of the 282(3.9%) hospitalized patients who had severe pneumonia confirmed by either chest radiography (CXR) or computed tomography (CT) received tocilizumab (Actemra). Polymerase chain reaction (PCR) viral markers of COVID-19 were positive in three cases. Hypoxemia and surrogate markers of cytokine storm improved after the prescription of tocilizumab (p=0.003 in all laboratory parameters). Two of the patients who received tocilizumab have been transferred to reference centers. No mortality or adverse reactions case was registered.

**Conclusion:** Our observational study demonstrated significant improvement in oxygen saturation, reduction in inflammatory markers – leukocytosis, CRP and D-dimers and 83% recovery without need for mechanical ventilation and no mortality in patients with COVID-19 with severe multilobar bilateral pneumonia and CT score 3-4 receiving tocilizumab in addition to standard treatment.

**Key words:** COVID-19, severe pneumonia, tocilizumab, cytokine storm, outbreak of pandemics, etiopathogenetic therapy, outcomes

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## Introduction

Coronavirus disease 2019 (COVID-19) is the infectious condition caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first identified during the outbreak of respiratory conditions in Wuhan City, Hubei 39 Province, China (1). It is characterized by large numbers of patients requiring medical care concurrently, resulting in overloaded public health and healthcare systems and, potentially, elevated rates of hospitalizations and deaths. On March 11, 2020, the WHO declared COVID-19 a global pandemic; so far, it is accepted as global emergency (2). On February 11, 2020, the Coronavirus Study Group of the International Committee on Taxonomy of Viruses announced an official designation for the novel virus: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (3).

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Clinical presentations of COVID-19 range from asymptomatic/mild symptoms to severe illness and mortality (4-6). Headache, sputum production, and diarrhea are less common. Williamson et al (6), in an analysis of 17 million patients, reaffirmed that severe COVID-19 and mortality were more common in males, older individuals, individuals living in poverty, Black persons, and patients with medical conditions such as diabetes, obesity, cardiovascular conditions, and severe asthma.

According to Chinese researchers, the clinical course was characterized by the development of dyspnea in 55% of patients and lymphopenia in 66% and all patients with pneumonia had abnormal lung imaging findings ((4, 7). Acute respiratory distress syndrome (ARDS) developed in 29% of patients and ground-glass opacities are common on computed tomography (CT) scans. (4, 7).

As the clinical course of disease progresses, patients may enter a hyperinflammatory phase with dysregulation of adaptive immune responses and further elevation of pro-inflammatory cytokines including interleukins (IL) (2, 6, 7), granulocyte-stimulating factor (G-CSF), interferon-gamma-inducible protein-10 (IFN-gamma) and tumor necrosis factor alpha (TNF-alpha). This event has been named “cytokine release storm” (CRS) (8). Based on this pathogenetic basis, implementation of tocilizumab, a monoclonal antibody against membrane bound IL-6 receptor was advocated for patients with COVID-19 and ARDS (9, 10).

In this retrospective analysis, we aimed to assess the clinical and laboratory outcomes of patients with severe pneumonia due to COVID-19 treated with tocilizumab.

## Methods

*Study population*

During the COVID-19 outbreak from July 6th to August 6th Scientific Research Institute of Heart Surgery and Organ Transplantation scheduled temporary infectious hospital (observation) in RIXON hotel for 50 beds.

In this period of time, 1382 patients visited our temporary hospital. Of these, 1100 patients were managed in outpatient care, and 282 were hospitalized.

All patients gave informed consent for examinations and treatment. No approval of Ethics Committee for retrospective studies is required in our institution.

*Study design*

Single-centered, observational, retrospective

*Baseline clinical examinations*

Baseline clinical (age, sex, comorbidity, complaints, duration of hospital stay) and laboratory, electrocardiography (ECG) data were collected from case histories of discharged patients.

The CURB 65 scale was used to assess the clinical severity of disease (Table 1) (11). Total points ≥3 were considered as severe forms of pneumonia.

During hospitalization period, body temperature data were highlighted before and after treatment. Fever was considered when body temperature exceeded 38 $^0$C.

*Radiological analysis*

The chest X-ray or chest CT were done whenever possible for all patients. CT data were assessed by CORADS and Chest CT classification systems (Table 2) (12, 13).

Chest CT score: Each lung was assessed individually, and depending on the extent of involvement by consolidation or ground-glass opacity a score of 0 to 4 points was given (0 - no involvement, 1 - < 5% involvement, 2. 5–25% involvement; 3 - 26–50% involvement; 4 - 51–75% involvement; and 5 - > 75% involvement). The overall score was the sum of points from both lungs.

**Table 1. CURB 65 scale for the assessment of pneumonia severity**

| Parameters | Points |
|---|---|
| **C**onfusion | 1 |
| Blood **U**rea nitrogen >19mg/dL | 1 |
| **R**espiratory Rate > 30 per min | 1 |
| **B**lood pressure: SBP<90, DBP<60 mm Hg | 1 |
| Age ≥ **65** yrs | 1 |
| SBP- systolic blood pressure, DBP- diastolic blood pressure | |

| Table 2. CORADS scale (COVID-19 Reporting and Data System) | | |
|---|---|---|
| CORAD grades | Likelihood of COVID-19 | CT findings |
| CORAD-1 | No | Normal or non-infectious abnormalities |
| CORAD-2 | Low | Abnormalities consistent with infections other than COVID-19 |
| CORAD-3 | Indeterminate | Unclear whether the COVID-19 is present |
| CORAD-4 | High | Abnormalities suspicious for COVID-19 |
| CORAD-5 | Very high | Typical COVID-19 |
| CORAD-6 | Positive PCR | |
| PCR- polymerase chain reaction | | |

*Laboratory analysis*

Immunoglobulins G and M for SARS CoV2 were analyzed through polymerase chain reaction for confirmation of COVID-19. Due to limited opportunity we could not directly measure IL-6 levels. Nevertheless, we assessed surrogate laboratory markers of cytokine release syndrome.

Oxygen level was assessed both invasively and noninvasively: arterial blood gas oxygen (ABG $PAO_2$) and oxygen saturation by pulse oximetry. Reference values: more or equal to 79 torr for (ABG PAO2) and more or equal to 95% for oxygen saturation ($SPO_2$).

Leukocyte count and differentials were assessed from common blood count. As a hallmark of infection we looked at lymphocytes and neutrophil bands. Reference values: 5-11.0 × $10^9$/L (for leucocyte count), 20-40% (for lymphocytes) and ≤6% (for neutrophil bands). Sampling of venous C-reactive protein was also performed with reference value: ≤10 mg/L.

Activated partial thromboplastic time (APTT) and D-dimer assays were also collected before and after treatment. Reference values: 30-40 s (for APTT) and < 250 ng/mL (for D-dimer).

*Criteria for the prescription of tocilizumab (Actemra) and standard treatment details*

Any hospitalized patient who had at least 2 of the following parameters were eligible for tocilizumab treatment: CURB 65 scale≥3points, CRP level≥50mg/l, D-dimer≥2000ng/ml, bilateral multilobar pneumonia documented by chest X-Ray or chest CT. Tocilizumab was prescribed in dose of 200mg/day for 3 days intravenously (total dose for each patient 600mg).

Standard therapy regimen:

-Supplemental oxygen therapy;

-Self-proning position 1:2 protocol (patients alternated 1 hour in recumbent, 2 hours in supine positions)

-Antibiotics, either monotherapy or combined regimen: either azithromycin (500mg/day for 5 days) or ceftriaxone (2.0 g /day for 10 days) or levofloxacin 500mg/day 6 days;

-Anticoagulants and anti-platelet drugs: either non-fractionated heparin (15000 IU/day), low-molecular weight heparin (fraxiparine 4000 IU/day) or rivaroxaban (Xarelto 15mg/day) combined with aspirin 75-100 mg/day or clopidogrel 75mg/day.

-Intravenous fluid infusion managed by one of the solutions: normal saline, 5% dextrose and Ringer solutions.

-Supportive and symptomatic therapy: gastroprotective H2-blockers (either omeprazole 40mg/day or pantaprazole 40mg/day), acetaminophen (500mg/single dose during fever) and ascorbic acid (up to 8.0 gr dose) intravenously

-Besides the standard therapy, all patients continued/started treatment according to comorbid conditions, e.g., insulin or antidiabetic drugs for diabetes, antianginal – for coronary artery disease, antihypertensive – hypertension, antiarrhythmic – arrhythmia, s etc.

*Statistical analysis*

We used SPPS 1.0.0.1406 (27th version 2018, IBM, USA) as a computing statistic tool. Categorical variables are depicted by absolute count and proportion whereas continuous variables are presented as mean and standard deviation. We used non-parametric Wilcoxon rank sum test for comparing the initial and post-treatment laboratory results. P vale <0.05 was accepted as statistically significant.

**Results**

*Baseline data on treatment options*

Tocilizumab use was indicated in 11 (3.9%) patients (out of 282) according to criteria developed by our physicians. No allergic reactions or other serious side effects were observed. All patients with and without tocilizumab prescription were managed by standard treatment and individual treatment according to comorbidities. All patients with and without tocilizumab prescription were managed by supplemental oxygen. There was no information about use of high-flow nasal cannula, non-invasive positive pressure and invasive mechanical ventilation. One patient (n=1) who received tocilizumab could not perform self-proning positions due to advanced congestive heart failure (NYHA IV functional class).

Due to limited opportunity of intensive care settings, patients have not been prescribed vasopressors or mechanical circulatory support modalities, including hemodialysis. In case of need for them, patients were transferred to reference centers for advanced management.

*Baseline demographic and clinical characteristics*

Due to inconclusive data (incomplete clinical, laboratory and radiologic reports) of patients who did not receive tocilizumab, we focused on baseline data of 11 patients in whom tocilizumab was prescribed. All known baseline and clinical data are shown in Table 3. In our small sampled study female patients prevailed: 7 (64%). Median age was 59 years.

The main complaints were registered as follows: fatigue 10 (90%), headache 9 (81%), dyspnea 8 (72%), fever 6 (54%) and cough 5 (45%) of patients. These complaints were observed simultaneously in almost all cases. After treatment, all complaints were halted or decreased significantly.

Data regarding the comorbid conditions was not available in 8 patients. Nevertheless, 3 combined conditions were registered.

*Outcomes*

The mean duration of hospital stay was 9.8 (4.2) days, median 10 days, range 4-18 days. Two patients were transferred to reference centers due to need for mechanical ventilation and acute coronary syndrome (severe COPD and unstable angina), whereas 9 patients were successfully discharged from temporary hospital after normalization of clinical-laboratory markers. During the hospital stay in RIXON observation, no mortality cases were registered. There were no available information regarding outcomes of patients in whom tocilizumab was not prescribed (including mortality, need for mechanical ventilation, discharge).

**Table 3. Baseline demographic and clinical findings**

| **Parameters** | **Results** |
|---|---|
| Sex, n(%) | Males: 4 (36%), Females: 7 (64%) |
| Age, years | Mean: 60.9 (9.3) Median: 59 |
| Complaints, n | Dyspnea 8, Fatigue 10, Headache 9, Fever 6, Cough 5 |
| CURB 65 score% | Severity 3: 5 (46%)<br>Severity 4: 4 (36%)<br>Severity 5: 2 (18%) |
| Comorbidities, n(%) | T2DM+EH 1 (9%)<br>UA+EH+T2DM 1 (9%)<br>VHD +AF+CHF 1 (9%)<br>COPD 1 (9%)<br>Non-available 7 (64%) |
| Duration of hospital stay, days | Mean 9.8 (4.2) Median 10 |
| Outcome | Discharged: 9 (82%)<br>Transferred: 2 (18%)<br>Mortality: 0 |

AF-atrial fibrillation, CHF-congestive heart failure, EH-essential hypertension, T2DM-type 2 diabetes mellitus, UA-unstable angina

*Electrocardiography and radiological data*

In two patients ST depression and atrial fibrillation was registered via electrocardiography (ECG), in other 9 cases ECG data were not found. Furthermore, there were no transthoracic echocardiography and lung ultrasound data.

Following table 4 shows radiological findings of our patients with comments. We could not compare pre- and post-treatment radiologic investigations due to lack of follow-up radiological data.

**Table 4. SARS-Cov-2 PCR markers, ECG and radiological findings of patients**

| Parameters | Results | Comments |
|---|---|---|
| SARS-Cov-2 PCR markers (IgG and IgM) | Positive: 3 (27%)<br>Negative: 8 (73%) | Most cases were PCR negative |
| ECG | ST depression: 1 (9%)<br>Atrial fibrillation:1 (9%)<br>n/a: 9 (82%) | Probably the ECG was not conducted for patients unless suspicion for cardiovascular involvement emerged |
| Imaging options | CR 2(18%)<br>CCT 9 (82%) | Both CR and CCT represented bilateral multilobar pneumonia |
| CORAD score | CORAD 4: 5 (45%)<br>CORAD 5: 4 (36%)<br>n/a: 2 (19%) | Both CORAD and CCT scores were depicted in CT protocols. However we could not find special severity indexes in CR protocols except the general conclusion.<br>Most patients had high likelihood of COVID-19 according to CT and grade 3 (25-75%) consolidation or ground-glass opacity on chest CT |
| CCT score | CT 3: 7(63%)<br>CT 2: 1 (9%)<br>CT 4: 1 (9%)<br>n/a 2 (19%) | |
| Pneumonia | Bilateral multilobar: 11 (100%) | All cases were represented by bilateral and multilobar involvement. |

CCT- chest computed tomography, CORAD – COVID-19 radiologic, CR-chest radiography, scoring, ECG-electrocardiography, RALE – radiologic assessment of lung edema

*Laboratory findings*

Only three cases were confirmed with laboratory viral markers: U07.1 (COVID-19, virus identified). Other cases were consistent with U07.2 diagnoses (COVID-19, virus not identified) (Table 4).

Analysis of laboratory data before and after treatment with tocilizumab (Table 5) demonstrated significant increase in oxygen saturation, decrease in body temperature, leucocyte count, lymphocytes and neutrophil band (all p=0.003). There was also marked reduction in CRP, and D-dimer after treatment with tocilizumab (p=0.003 for both). There was an increase in APTT (p=0.003). Arterial oxygen pressure was not compared(due to invalid input data).

**Table 5. Laboratory findings before and after treatment**

| Parameters | On admission | After treatment | p |
|---|---|---|---|
| SPO2, % | 53 (4) | 87 (2) | 0.003 |
| Body temperature, $^0$C | 38.7 (0.4) | 37.1 (0.2) | 0.003 |
| ABG PaO2, torr | less than 10 | 66.3 (6.3) | n/a |
| Leucocytes, (x10^3/L | 11.2 (1.2) | 5.7 (0.9) | 0.003 |
| Lymphocytes, % | 52.0 (5.8) | 22.7 (5.8) | 0.003 |
| Neutrophil bands, % | 11.5 (2.2) | 3.1 (1.5) | 0.003 |
| CRP, mg/L | 66.3 (9.1) | 11.0 (3.3) | 0.003 |
| APTT, s | 22.7 (4.0) | 38.1 (6.8) | 0.003 |
| D-dimer, ng/ml | 2236 (607.0) | 740.9 (249. 8) | 0.003 |

ABG PaO2 - arterial blood gas oxygen, APTT – activated partial thromboplastin time, CRP – C-reactive protein, n/a – non-available SPO2 - oxygen saturation; Data are presented as mean (SD)

## Discussion

*Etiopathogenic treatment of infection*

For today, we still do not have strong evidence on etiopathogenic treatment of COVID-19. Various pharmacological agents, including antiretroviral, anti-EBOLA, antimalarial and anti-inflammatory drugs are prescribed as off-label use hopefully. Final report on Remdesivir states the superiority of antiretroviral drug to placebo in shortening the time to recovery in adults (14). With respect to dexamethasone, the preliminary results of RECOVERY trial showed the decreased 28-day mortality in patients who received respiratory support (14, 15). Nonetheless, disease-modifying target drugs of autoimmune conditions, namely IL-6 and IL-1 inhibitors justified themselves efficacious in pathogenetic treatment of COVID-19 by reducing the severity of the cytokine storm, although higher and prolonged doses increased superinfection risks (10, 16, 17).

Regarding to Tocilizumab, Roche's phase III EMPACTA achieved its primary goal: patients with COVID-19 associated pneumonia who received Actemra/RoActemra plus standard of care were 44% less likely to progress to mechanical ventilation or death compared to patients who received placebo plus standard of care (log-rank p-value = 0.0348; HR (95% CI) = 0.56 (0.32, 0.97)) (10). Another study conducted on severe pneumonic patients revealed the superiority of tocilizumab treatment in reducing the risk of invasive ventilation and mortality in contrast to standard care (supplemental oxygen, hydroxycholoroquine, azithromycin, antiretrovirals, low-molecular weight heparin) (18). According to Parr (19), current trials could not show exact efficacy due to inherent limitations. Nonetheless, in trials the potential role of Tocilizumab in the management of COVID-19 patients was clarified in contrast to observational studies (19).

*Findings of our study*

Despite the restricted sample size with tocilizumab and incomplete follow-up, we found good clinical-laboratory results. The significant improvement of hypoxemia and decreased levels of inflammatory markers, such as leukocytosis, CRP and D-dimer indicate the efficacy. Most importantly, there was only one case of need for mechanical ventilation and there were no early deaths, which is consistent with literature review (17, 18).

*Limitations of our study*

Our study had several limitations, including the small sample size, the lack of control groups, study design issues, the lack of appropriate follow-up. Furthermore, we could not obviously renounce the inevitability of bias and confounders. For reliable assessment of efficacy and safety of tocilizumab, we should define inclusion and exclusion criteria, compare with control group and exclude the potential impact of standard treatment regimen and comorbid issues. Furthermore, we should conduct survival analyses for further investigations.

## Conclusion

Our observational study demonstrated significant improvement in oxygen saturation, reduction in inflammatory markers – leukocytosis, CRP and D-dimers and 83% recovery without need for mechanical ventilation and no mortality in patients with COVID-19 with severe multilobar bilateral pneumonia (CT score 3-4) receiving tocilizumab in addition to standard treatment**.**

Currently, we do not have evidence-based data on etiopathogenetic treatment of COVID-19. IL-6 inhibitor, tocilizumab (Actemra) justified itself well for the use of severe COVID-19 patients from the point of view of immunopathology. It has been proven to be effective in clinical-laboratory improvement, as well as reducing the risk of mechanical ventilation and mortality. Hopefully we are waiting the outcomes of the large scale on-going trials to fully understand the role of tocilizumab in COVID-19.

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